Conferences and Reviews

Fever, Rash, and Arthritis in a Woman With Silicone Gel Breast Implants

Discussant
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Case Presentation

The patient, a 44-year-old woman, was transferred to the Stanford University Medical Center, Palo Alto, California, for the evaluation of fever, rash, and arthritis. Her medical history began in 1990 when bilateral silicone gel breast implants were inserted for cosmetic reasons. These implants were replaced in January 1996, when capsular contracture and substantial hardening developed. About three weeks after the operation, the patient noted a rash under her left breast that spread rapidly to her torso and extremities. The rash was described as pink, maculopapular, nonconfluent, and mildly pruritic. She noted that it waxed and waned but usually was most prominent in the evenings.

In April 1996 she noted pain, stiffness, and swelling in the wrists, knees, ankles, and the interphalangeal joints of her hands. A persistent sore throat developed, and she had intermittent fevers to 38.9°C (102°F) that were more frequent and severe later in the day and often were accompanied by the rash. She treated herself with ice packs and topical emollients but achieved only minor relief.

In August 1996 the patient sought advice from her primary care physician when, in addition to the persistent rash and arthritis, her temperature rose to 40°C (104°F). She was admitted to an outside hospital for evaluation. Laboratory evaluation at that time was notable for a leukocytosis (leukocyte count, 23×10^9 per liter [23,000 per mm^3]), anemia (hematocrit, 0.30 [30%]), and elevated aminotransferase values (aspartate and alanine aminotransferase, both 120 units per liter). In addition, her serum alkaline phosphatase (400 units per liter) and γ-glutamyltransferase (GGT) levels were elevated. Biopsy of a left axillary lymph node showed only reactive hyperplasia. She had an extensive evaluation by a gastroenterologist in which an abdominal computed tomographic scan showed a 3-cm mass in the liver that was consistent with a hemangioma, and mild hepatic and splenic enlargement was noted. The results of colonoscopy, endoscopic retrograde cholangiopancreatography, and small bowel enteroclysis were all normal, and a viral hepatitis panel was negative. A liver biopsy specimen revealed a nonspecific inflammatory infiltrate.

All blood and stool cultures were negative for bacteria, fungi, fastidious organisms, ova, and parasites. A Venereal Disease Research Lab test, a rapid plasma reagin test, and serologic tests for Epstein-Barr virus, cytomegalovirus, Borrelia species, and parvovirus were all negative, and a lumbar puncture revealed no abnormalities.

Given the lack of any obvious infection, the patient's physicians searched for remote possibilities. She had emigrated from Korea (albeit 20 years previously with no recent foreign travel), and therefore scrub typhus was added to the list of possible diagnoses; the results of serologic tests for typhus returned negative as well. A gallium scan was done and showed increased uptake in the right frontal lobe of the brain, but findings were otherwise normal. Subsequent magnetic resonance imaging (MRI) of the brain revealed a parafalcine meningioma thought to be incidental. Despite the negative serologic studies, she was empirically treated with several antibiotic agents, including doxycycline, ofloxacin, vancomycin, clarithromycin, and ampicillin. Her fever did not resolve.

Immunologic tests revealed only an erythrocyte sedimentation rate (ESR) of 60 to 80 mm per hour and a low rheumatoid factor of 30 units by latex agglutination

*See also "Scleroderma and Silicone Breast Implants" by Donald Whorton, MD, MPH, and Otto Wong, ScD, on pages 159–165 and "Plaintiffs, Defendants, Lawyers, and Lawyers: Facts and Rumors About Silicone" by John S. Sergent, MD, on pages 182–183 of this issue of THE WESTERN JOURNAL OF MEDICINE.

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ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
ASO = antistreptolysin O
DIC = disseminated intravascular coagulopathy
ESR = erythrocyte sedimentation rate
FDA = US Food and Drug Administration
GGT = γ-glutamyltransferase
MRI = magnetic resonance imaging
NSAID = nonsteroidal anti-inflammatory drug

(normal <40). An anti–smooth muscle antibody titer was positive at 1:80, but on repeat study was found to be negative. A comprehensive list of other negative assays is listed in Table 1. A hematologic workup for the patient's anemia included a bone marrow biopsy that showed both a normal marrow population and flow cytometric analysis of cells. The marrow had mildly decreased iron stores, and culture was negative for pathogens. She was empirically started on a short course of glucocorticoids; she subjectively improved and was discharged home.

In November 1996 the patient noted the return of the rash; temperatures from 39.4°C to 40.0°C (103°F to 104°F); bilateral arthritis involving her hands, wrists, elbows, and knees; and new symptoms of shortness of breath and cough. Again she received an exhaustive workup that was notable for new pleural effusions on physical examination and on the chest x-ray film. She was admitted to an outside hospital, and thoracentesis was done, which identified only a transudate that was culture-negative. An MRI of her thorax revealed an area of probable inflammation (3 cm in diameter) under the left breast implant. The ESR remained elevated in the range of 80 to 90 mm per hour, a ferritin level was 7,000 µg per liter (7,000 ng per ml), and an antistreptolysin O (ASO) titer was 170 units (normal ≤100). On hospital day 2, a regimen of methylprednisolone sodium succinate, 1 gram per day for three days, was started.

On the third hospital day, progressive mental status changes developed, categorized by the patient's physicians as severe encephalopathy, followed by hypoxemia and respiratory acidosis. An electroencephalogram showed global suppression without evidence of seizure phenomenon. An MRI of the head showed the parafalcine meningioma noted previously and no other abnormalities. Analysis of fluid from the lumbar puncture elicited the following values: protein, 2.78 grams per liter (278 mg per dl); glucose, 7.9 mmol per liter (142 mg per dl); leukocyte count, 22×10^6 per liter (22 cells per mm^3) (neutrophils, 0.62 [62%]; lymphocytes, 0.28 [28%]; monocytes, 0.10 [10%]); and erythrocyte count, 11×10^9 per liter (11,000 per mm^3). Gram's stain and culture were negative. Intravenous immune globulin therapy was then instituted at 400 mg per kg a day for 5 days. During this process the patient also had anasarca, worsening renal function (serum creatinine level, 186 µmol per liter [2.1 mg per dl]), proteinuria, low-grade disseminated intravascular coagulopathy (DIC), and pulmonary infiltrates on chest x-ray film. Plasmapheresis was initiated, and she was given fresh frozen plasma and cryoprecipitate. This resulted in an anaphylactic reaction that was treated with additional glucocorticoid therapy. The patient's mental state gradually improved, and she was continued on a regimen of methylprednisolone at 100 mg three times a day with abatement of the rash, fevers, and arthritis. Other studies included an elevated immunoglobulin E level (765 µg/l), a mildly abnormal C1q binding assay for immune complexes, and eosinophilia (4×10^6 per liter [400 per mm^3]). A second liver biopsy was unremarkable. The findings of a skin biopsy were consistent with leukocytoclastic vasculitis. The patient was then transferred to the Stanford University Medical Center for further evaluation.

TABLE 1.—*Negative and Normal Results of Autoimmune Workup*

Laboratory Study	*Finding*
Antinuclear antibody	Negative
Anti–double-stranded DNA antibody	Negative
Ribonuclear protein antibody	Negative
Anti–SSA (Ro)	Negative
Anti–SSB (La)	Negative
Anti–neutrophil cytoplasm antibodies	Negative
C3	Normal
C4	Normal
Total hemolytic complement (CH_{50})	Normal
C1q binding assay	Normal
Raji cell assay	Normal
Antimitochondrial antibody	Negative
Free thyroxine	Normal
Thyroid-stimulating hormone	Normal
Cryoglobulins	Negative

The patient was admitted to the medicine service at Stanford University. Physical examination and laboratory findings at presentation are listed in Tables 2, 3, and 4. At the time of the transfer, her chest x-ray film showed some improvement from previous films, but bilateral pleural effusions (left greater than right) persisted. There were no focal infiltrates. Initially her methylprednisolone treatment was continued at 100 mg given intravenously every 8 hours until all her data could be assimilated and the case reconstructed. Given her degree of anasarca, she was aggressively diuresed. A second bone marrow biopsy showed hypercellularity, numerous normal megakaryocytes, and decreased iron stores. She continued to have evidence of low-grade DIC with elevation in d-dimers and a low fibrinogen level; however, she never bled. An erythrocyte folate level, serum B_{12} level, haptoglobins, Coombs' test, and reticulocyte count were all normal. By hospital day 3, her steroid dosage was being tapered and her edema had lessened dramatically. The patient continued to improve

TABLE 2.—*Results of the Physical Examination*

Category	*Finding*
General	Patient appeared fatigued and edematous but not in distress
Vital signs	Temperature 36.8°C, blood pressure 140/78 mm of mercury, pulse 90 beats per minute, respiratory rate 16
Head	Normocephalic and atraumatic; pupils equal, round, reactive to light and accommodation; funduscopy revealed some narrowing of vessels; extraocular muscles intact and conjunctivae moist and noninjected; no evidence of patchy alopecia
Mouth	No evidence of thrush or lesion; mucous membranes were moist
Neck	Carotids had 2+ pulses without bruit; jugular venous distension to 8 cm above the sternal notch; thyroid gland was not palpable
Nodes	Bilateral axillary and anterior cervical chain lymphadenopathy 1 to 2 cm, tender
Breasts	Silicone breast implants bilaterally, with no erythema, warmth, or hardening
Lungs	Dullness to percussion in the bases bilaterally; decreased breath sounds in bases and crackles in the lower half of the lungs bilaterally to auscultation
Heart	Normal rate, regular rhythm, normal S1 and S2, no murmur, gallop, or rub audible
Abdomen	Liver edge palpable 2 cm below the right costal margin; stool Hemoccult-negative
Extremities	Anasarca with pitting edema in all four extremities
Neurologic	Nonfocal, with brisk reflexes, normal strength, normal gait and sensation
Joints	No evidence of synovitis with normal range of motion in all joints
Skin	No evidence of rash or excoriation

and was discharged to home ambulating and doing well, never having manifested fever, rash, or arthritis during her hospital stay. She was discharged on a slow prednisone taper from 60 mg per day. At her last visit to the clinic, 3 months after hospital discharge, she was taking 15 mg per day of prednisone and was asymptomatic.

Summary

Despite the long time course in this patient's presentation, a number of salient features were recurrent throughout her clinical course. Initially, and recurrently, a subtle rash developed primarily on the patient's torso. She had spiking fevers that were often more prominent in the evenings and seemed to herald the onset of the rash. Sore throat and arthritis also became commonplace for her. Her course waxed and waned over several months, and despite seeking medical care, she did not improve. The process was also accompanied by adenopathy and hepatosplenomegaly.

Although the patient's condition improved after a short course of glucocorticoids in the autumn, her illness then took on a more aggressive form. She had the development of pleural effusions, aseptic meningitis, anemia, leukocytosis, altered mental state, alterations in renal function, and edema. Not long after, she progressed to have hypofibrinogenemia, low-grade disseminated intravascular coagulopathy, and transient thrombocytopenia. This disorder precipitated several admissions to a hospital and culminated with aggressive intervention with high-dose glucocorticoids, intravenous immune globulin, and plasmapheresis.

TABLE 3.—*Chemical Laboratory Findings*

Test	*Value, SI Units* (Conventional Units)*
Electrolytes	
Sodium, mmol/liter	140 (140)
Potassium, mmol/liter	3.8 (3.8)
Chloride, mmol/liter	106 (106)
Carbon dioxide, mmol/liter	24 (24)
General chemistry	
Glucose, mmol/liter (mg/dl)	9.7 (174)
Urea nitrogen, mmol/liter (mg/dl)	16.8 (47)
Creatinine, µmol/liter (mg/dl)	115 (1.3)
Calcium, mmol/liter (mg/dl)	2.05 (8.2)
Phosphorus, mmol/liter (mg/dl)	0.97 (3.0)
Total protein, grams/liter (grams/dl)	54 (5.4)
Albumin, grams/liter (grams/dl)	30 (3.0)
Globulin, grams/liter (grams/dl)	24 (2.4)
Bilirubin, total, µmol/liter (mg/dl)	6.8 (0.4)
Aspartate aminotransferase, units/liter	52
Alanine aminotransferase, units/liter	53
Alkaline phosphatase, units/liter	63
Lactate dehydrogenase, units/liter	807
Creatine kinase, units/liter	35
Cholesterol, mmol/liter (mg/dl)	2.92 (113)
Special studies	
Rheumatoid factor, units/liter	<10
Ferritin, µg/liter (ng/ml)	985 (985)

*SI units are Système International units.

TABLE 4.—*Hematologic Laboratory Findings*

Test	*Value, SI Units* (Conventional Units)*
Hematocrit, factor of 1 (%)	0.21 (21)
Hemoglobin, grams/liter (grams/dl)	67 (6.7)
Platelets, $\times 10^9$/liter (10^3/mm^3)	123 (123)
Leukocytes, $\times 10^9$/liter (/mm^3)	5.9 (5,900)
Erythrocyte sedimentation rate, mm/hour	0
Differential cell count	
Neutrophils, factor of 1 (%)	0.82 (82)
Bands, factor of 1 (%)	0.01 (1)
Lymphocytes, factor of 1 (%)	0.09 (9)
Monocytes, factor of 1 (%)	0.08 (8)
Mean corpuscular volume, fl (μm^3)	80 (80)
Red cell distribution width, factor of 1 (%)	0.21 (21)
Coagulation	
Partial thromboplastin time, sec	32.8
Prothrombin time, sec	13.9
International normalized ratio	1.3
D-Dimer, μg/l	500 to 1,000
Fibrinogen, grams/liter (mg/dl)	0.98 (98)
Reptilase, sec	19.9
Thrombin time, sec	18.3

*SI units are Système International units.

Discussion

MARK GENOVESE, MD: Could the disorder from which the patient suffers be silicone-related connective tissue disease? A widespread perception is that there is a direct relationship between silicone breast implants and connective tissue diseases. There are many reasons for this. Reports of cases of connective tissue diseases developing associated with silicone implants began to appear in the 1960s. This association first came into the public spotlight in December 1990, when CBS television news broadcast a segment titled "Hazards of Silicone Breast Implants." Since then silicone has drawn widespread attention in both lay and professional publications. Responding to growing concerns about the safety of silicone breast implants, the US Food and Drug Administration (FDA) in January 1992 announced a moratorium on the use of silicone gel breast implants until more information could be gathered about their safety. This moratorium was lifted in April 1992; at that time, however, the FDA acted to restrict the availability of silicone gel implants to controlled clinical trials.[1] In a class action lawsuit heard in the state of Alabama, the manufacturers of the silicone gel breast implants agreed to pay more than $4 billion to symptomatic implant recipients.

Given the perception of an association between silicone and connective tissue diseases, it is important to review the data to better facilitate an understanding of the problem. In the following section, several aspects of the problem will be addressed: the reported local reactions to silicone; the issues raised by the larger epidemiologic studies; and the symptoms, signs, and laboratory data frequently reported from symptomatic patients who have received silicone breast implants. These findings should be examined in the context of the case reported here. As well, no diagnosis can be arrived at without first working through a differential diagnosis, and I will do that, paying particular attention to the workup this patient received. Finally, I will discuss the probable diagnosis in this case and its implication for the treatment and prognosis of this patient.

Clearly local reactions to silicone do occur. Silicone is a polymer made through several chemical steps from the element silicon. The direct administration of silicone oils was popular in cosmetic surgery, particularly in the 1960s and 1970s. This practice continued for years, even after reports began to suggest that these oils led to local granulomatous reactions. In addition, these oils tended to migrate under the influence of gravity, leading to compression neuropathies and painful granulomas.[2] The most common local reaction to silicone breast implants is known as capsular contraction. This is a fibrotic reaction that occurs around the prosthetic envelope and leads to capsular shrinkage. It occurs to some degree in all patients with implants, leading to fibrotic changes palpable as firmness surrounding the breast implant.[3] In its severe form, there is extensive hardening of the surrounding breast tissue, severe tenderness, and a need for explantation. In addition to the local reaction to the silicone implant capsule, silicone oils may bleed through the cover of an intact silicone gel implant, causing local fibrotic and granulomatous changes.[3,4] If an implant ruptures, the silicone gel can produce local granulomata, fibrosis, and in some cases, a distant local reaction due to migration of the silicone.

A recently published (March 1997) population-based study looked at complications of silicone breast implantation that lead to additional surgery. Investigators reviewed the records of 749 women who lived in Olmsted County, Minnesota, and had undergone breast implantation at the Mayo Clinic between 1964 and 1991.[5] Of the 749 women, 208 (28%) underwent 450 additional implant-related operations. Of those, 91 were anticipated to be due to staged procedures or for changes related to size or cosmetic appearance. Of the 450 procedures, however, 359 were found to be related to complications from the previous breast implantation. The most common problem was related to substantial capsular contracture, affecting 131 of the 749 women (17.5%). Implant rupture and hematoma each resulted in 43 women requiring additional surgery. These data correlate with previous data and suggest that local complications related to silicone breast implants are common.[5]

In 1994, a review was published of all previously published case reports of associations between silicone and connective tissue diseases.[6] The authors reviewed both injectable substances and breast implants. A total of 293 patients were identified who had rheumatic symp-

toms after receiving silicone gel-filled implants. Of this group, 38 patients were given a diagnosis of scleroderma. Another 221 patients with gel-filled implants had symptoms that did not meet criteria for a diagnosable connective tissue disease. After reviewing animal studies, silicone immunogenicity, and the case reports, the authors came to the conclusion that silicone may elicit a local inflammatory response. The clinical, immunologic, and epidemiologic evidence, however, suggested no association between silicone and either a known or a novel connective tissue disease.[6]

The question plaguing practitioners and patients has not been whether silicone may cause a local inflammatory or granulomatous reaction, but whether silicone itself is a primary antigen or stimulus that leads to a systemic autoimmune or connective tissue disorder. What are the epidemiologic data? In 1994 a study was published that attempted to establish the risk of connective tissue diseases after breast implantation.[7] In this study in Olmsted County, Minnesota, 749 recipients of breast implants inserted between January 1964 and December 1991 were compared with 1,498 age-matched control women. Five cases of definite connective tissue disease were identified in the implant group, and ten cases were found in the control group. The conclusion was that there was no evidence of an association between silicone breast implants and connective tissue disease. In 1995 the results of the Nurses' Health Study cohort were published.[8] This study included 87,501 women, and of those, 1,183 had breast implants. With the use of questionnaires, it was determined that 516 women in this cohort of more than 87,000 had a definite connective tissue disease. Of these, only three in the group of 1,183 women with implants had a definite connective tissue disease, and all three had rheumatoid arthritis. No association was found between silicone breast implants and connective tissue diseases. In 1996 the FDA published a review of reported complications of silicone breast implants.[9] Cohort, case-study, and cross-sectional studies were reviewed. Study design, conclusions, and flaws were all summarized with the goal of addressing the reported relation between silicone and connective tissue diseases. The following conclusions were drawn[9(p 744)]:

> Information is insufficient to adequately advise women who currently have or are seeking to obtain breast implants about the overall risk of these devices. No epidemiologic study has indicated that the rate of well-defined connective tissue disease or breast cancer has greatly increased in women with silicone breast implants, but no studies have ruled out a moderately increased risk for these diseases. No studies have adequately addressed the crucial issue of local complications such as rupture and capsular contracture, although evidence increasingly points to a higher risk for rupture as implants age.

Available epidemiologic data suggest that there is no clear causal relationship between silicone breast implants and systemic connective tissue diseases. But is it possible that the patient in the case presented here does suffer from a silicone-related disorder? How well do her symptoms and signs correspond to those in published case series and anecdotal reports of silicone-related connective tissue disease?

The symptoms most often reported in symptomatic recipients of silicone breast implants include fatigue, arthralgia, and sicca-like symptoms. Data shown in Table 5 are representative. Similarly, the most common clinical signs reported in the same series (Table 6) included telangiectasias, erythema of the chest wall, and carpal tunnel syndrome.[10] From the data in Table 7, it can be seen that a spectrum of symptoms, signs, and laboratory data are reported between case series.[11] A careful review of the case report would suggest that the patient had few of the symptoms and signs outlined in Table 5 or Table 6 and few of the abnormal laboratory values listed in Table 8 during the course of her illness. This patient does not seem to fit the described profile of silicone-related connective tissue disease.

Part of the difficulty in establishing an association between silicone breast implants and connective tissue diseases has been that most of the symptomatic implant recipients fail to meet diagnostic criteria for known rheumatologic illnesses. Some authors have suggested that the constellation of symptoms and signs similar to those listed in Tables 5 and 6 could represent a new syndrome.[10–12] The vast spectrum of symptoms, signs, and laboratory tests that has been reported, however, and the differences among case series (Table 7) make it difficult to assign a single diagnostic syndrome. Although epidemiologic studies have not been designed specifically to address this issue, no study published to date has demonstrated any support for this theory. A recently published study looked for a relationship between breast implantation and connective tissue diseases.[13] In 1983,

TABLE 5.—*Symptoms in Patients With Silicone Breast Implants, n = 176*

Symptoms	*No. Patients (%)*
Chronic fatigue	135 (77)
Cognitive dysfunction	114 (65)
Arthralgia	98 (56)
Dry mouth	93 (53)
Dry eyes	88 (50)
Alopecia	71 (40)
Dysphagia	62 (35)
Photosensitivity	55 (31)
Myalgia	42 (24)
Raynaud's phenomenon	42 (24)
Serositis	30 (17)

Adapted from Solomon.[10]

TABLE 6.—*Physical Signs in Patients With Silicone Breast Implants, n = 176*

Signs	*No. Patients (%)*
Telangiectasias	105 (60)
Erythema of chest wall	99 (56)
Carpal tunnel syndrome	83 (47)
Petechiae	81 (46)
Enlarged lacrimal glands	45 (26)
Tender thyroid	38 (22)
Enlarged thyroid	37 (21)
Enlarged parotid	31 (18)

Adapted from Solomon.[10]

an inception cohort was established to observe the outcome of patients with early signs and symptoms of undifferentiated connective tissue diseases. A total of 410 subjects were enrolled between 1983 and 1987. Of the 410 patients, 197 satisfied criteria for specific connective tissue diseases: rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, or polymyositis or dermatomyositis. The remaining 213 patients were classified as having undifferentiated disease. Of the 410 patients, 323 were women. Of this group, only three had undergone breast implantation, one of whom had symptoms before implantation. All three women were classified in the undifferentiated group. The data failed to confirm any relationship between early symptoms of differentiated or undifferentiated connective tissue diseases and breast implants.[13]

If the patient in the case presented here does not have a connective tissue disease related to her silicone breast implants, what is her illness? First is the possibility of an infectious cause. After the initial evaluation, including Gram's stains and cultures, was negative, the likelihood of a bacterial infection—that is, perioperative wound infection, endocarditis, sepsis—seemed less likely. Attention then turned to more fastidious organisms such as mycobacteria. This patient showed no evidence of tuberculosis by skin tests (purified protein derivative), sputum tests, or bone marrow examination. Viral, parasitic, and spirochetal causes were considered. She had negative serologic tests for parvovirus B19, cytomegalovirus, and Epstein-Barr virus; tests for ova and parasites, malaria, rapid plasma reagin, and Lyme titer were all negative. Given her Asian ethnicity, scrub typhus was also considered and ruled out.

A lymphoproliferative process was also considered. Although lymphadenopathy and persistent abnormalities were found in the blood count (leukocytosis, thrombocytosis, and anemia), lymph node and bone marrow biopsies failed to confirm those suspicions. Given the presence of obvious organomegaly and abnormal results on liver function tests, the differential diagnosis included viral and autoimmune hepatitis, sclerosing cholangitis, and primary biliary cirrhosis. Numerous imaging studies, biopsies, and endoscopic retrograde cholangiopancreatography failed to shed light on the underlying cause of this patient's persistent illness.

Attention was then focused on diffuse connective tissue diseases. First thoughts usually include systemic lupus erythematosus, rheumatoid arthritis, and vasculi-

TABLE 7.—*Clinical Findings From Several Series of Silicone Implant Recipients*

Findings	*Vasey*	*Solomon*	*Freundlich*	*Borenstein*	*Total*
Patients, no.	50	176	50	100	376
Fatigue, %	84	77	88	91	83
Arthralgias, %	60	56	74	69	62
Myalgias, %	84	24	74	62	49
Cognitive dysfunction, %	—	65	—	13	46
Xerostomia or sore throat, %	—	53	50	26	44
Alopecia, %	—	40	38	35	38
Skin rash, %	10	46	36	15	36
Adenopathy, %	38	—	44	30	35
Arthritis, %	42	—	42	21	31
Fever, %	10	—	26	31	23
Raynaud's phenomenon, %	14	24	24	8	20
Antinuclear antibody, no. positive/no. tested (%)	11/41(26)	44/176 (25)	10/50 (20)	22/84 (26)	25
Elevated ESR, no. positive/no. tested (%)	7/40 (36)	57/176 (32)	4/50 (8)	14/76 (18)	24
Rheumatoid factor, no. positive/no. tested (%)	5/33 (15)	5/176 (3)	10/50 (20)	9/71 (12)	9

ESR = erythrocyte sedimentation rate
Adapted from Borenstein.[11]

TABLE 8.—*Laboratory Findings in Patients With Silicone Breast Implants*

Laboratory Findings	*Patients, %*
Erythrocyte sedimentation rate >25 mm/h	32
Immunoglobulin (Ig) M elevated >2.8 grams/liter (>280 mg/dl)	28
Antinuclear antibody ≥1:40	25
IgA elevated >4.5 grams/liter (>450 mg/dl)	8
Antimicrosomal antibody	6
IgG elevated >18 grams/liter (>1,800 mg/dl)	4
Rheumatoid factor >40	3
Anti-SSB (La)	2
Anti-SSA (Ro)	1

Adapted from Solomon.[10]

TABLE 9.—*Joint Involvement in Patients With Adult-Onset Still's Disease, n = 62*

Joint Involved	*No. Patients (%)*
Knee	51 (82)
Wrist	45 (73)
Ankle	34 (55)
Proximal interphalangeal	29 (47)
Elbow	27 (44)
Shoulder	25 (40)
Metacarpophalangeal	22 (35)
Metatarsophalangeal	11 (18)
Hip	7 (11)
Distal interphalangeal	6 (10)
Interphalangeal	2 (3)
Temporomandibular	2 (3)

Adapted from Pouchot et al.[19]

tis. None of these fit the clinical picture. The patient was negative for antinuclear antibody (ANA) and failed to meet the clinical or research criteria for systemic lupus erythematosus.[14] Rheumatoid arthritis and vasculitis did not adequately explain her manifestations or clinical course. More remote possibilities were considered, including parvovirus B19, cryoglobulinemia, and serum sickness, but the clinical presentation and laboratory test results did not fit any of these either. Rheumatic fever was a possibility, but the patient failed to meet Jones criteria for the diagnosis of rheumatic fever.[15]

One connective tissue disease, however, appears to be a probable diagnosis in this woman: adult-onset Still's disease. This disorder is a systemic inflammatory illness accompanied by the hallmark signs of spiking fever, rash, and polyarthritis.[16] The symptoms and signs are identical to those seen in children with systemic juvenile-onset rheumatoid arthritis or Still's disease. The mean age of onset of the adult version is 29.9 years plus or minus 12.4 years, and it affects both sexes equally.[17] The mean delay in arriving at the diagnosis may be as long as 16 months.[18] The clinical features commonly include high spiking fever (often accompanied by a sore throat); arthritis; and a subtle, fleeting, erythematous salmon-colored rash typically referred to as "evanescent." On occasion, patients may present with only a rash and fever. Both often become more prominent in the evenings. The rash typically involves the torso and extremities.[16] Although classically described only as maculopapular, the rash may be pruritic 30 to 40% of the time.[18,19]

Musculoskeletal manifestations are present at some point in virtually every patient with adult-onset Still's disease. In addition to arthralgia and myalgia, oligoarticular or polyarticular arthritis is almost always found. It commonly affects the knees, wrists, ankles, and proximal interphalangeal joints and less commonly the hips and shoulders (Table 9).[16,20] The accompanying synovitis is usually mild and transient, although a few patients have had measurable radiographic progression of arthritis. Of these, most had a good functional prognosis.[16,18] Carpal ankylosis may occur occasionally and has been described as a diagnostic sign in adult Still's disease.[16,20–22] Other patients may have ankylosis of the cervical spine. Synovial fluid analysis often reveals a high leukocyte count with a predominance of neutrophils.[19,20,22]

Other common symptoms and signs appear with adult-onset Still's disease (Table 10). A persistent or waxing and waning sore throat is common; lymphadenopathy and hepatosplenomegaly are among these, as is serositis (such as pleuritis and pericarditis).[17,19,20,23] Less common manifestations are listed in Table 11.

Do data from the laboratory evaluation help to confirm a diagnosis of Still's disease in adults (Table 12)? Patients frequently will show increases in the ESR, leukocytosis with a predominance of neutrophils, and normocytic, normochromic anemia.[16] Hepatocellular dysfunction is common; aminotransferase levels are frequently elevated, and patients occasionally have elevated alkaline phosphatase and GGT levels.[18,20,21] Four-fifths of patients will have difficulty with synthetic liver function leading to low serum albumin levels and coagulopathy with elevation in the international normalized ratio (INR).[20] Still other patients will become hypofibrinogenemic, and mild DIC and occasionally transient thrombocytopenia will develop.[17,19,22,24] The ASO titers may be mildly elevated, but ANA and rheumatoid factor are normal or only slightly abnormal. More recently, serum ferritin values have been found to be markedly elevated in patients with Still's disease, with values sometimes exceeding 20,000 µg/l.[17,25] Often the levels will exceed 10 times the normal value and have been shown to correlate with disease activity.[17,26]

How is the diagnosis of adult-onset Still's disease made? It is a clinical diagnosis based on a constellation of symptoms and signs and usually is made by exclu-

TABLE 10.—*Clinical Manifestations of Adult-Onset Still's Disease, n = 288*

Manifestations	*Patients, %*
Arthralgia	99.6
Fever ≥39°C (≥102°F)	95.7
Arthritis	94.3
Typical rash	88.5
Lymphadenopathy	60.3
Sore throat	57.9
Splenomegaly	51.7
Hepatomegaly	40.6
Weight loss ≥10%	38.3
Deforming arthritis	31.0
Pericarditis	27.8
Pleuritis	24.6
Abdominal pain	13.2
Pneumonitis	12.8
Renal involvement	10.7

Adapted from Ohta et al.[17]

sion. Paramount is the exclusion of other infectious, inflammatory, and neoplastic diseases as previously outlined. Patients often will present in their third or fourth decade of life with persistent fever, rash, and arthralgia or arthritis.[16] A patient will often have a sore throat and evidence of lymphadenopathy and hepatosplenomegaly. The most specific finding is the evanescent skin rash that is more obvious later in the day.[27] The laboratory abnormalities are nonspecific.

Unfortunately, the cause of Still's disease remains unknown. Although infectious causes, particularly viral (such as rubella or echovirus), have frequently been proposed, studies to date have failed to elicit any conclusive correlations. Investigators have also focused on a possible non-necrotizing, immune complex–mediated vasculitis; however, complement assays and skin biopsies have not adequately supported this theory.[21] Genetic predispositions have also been postulated. Investigators have examined HLA genotypes, but no consistent correlations have been established.[19,21]

Initial criteria for the diagnosis of adult-onset Still's disease were proposed by Bywaters in 1971 in a classic article discussing Still's disease in adults; they included high temperatures, transient rash, and arthritis.[16] Several authors since then have created their own variations on these criteria.[22,23,28,29] An effective set of criteria for diagnosis is listed in Table 13.[27] These were established by assessing the most common clinical features in 90 cases of Still's disease and comparing them with the clinical features of 267 control patients with other autoimmune or connective tissue diseases. In this series, all criteria were discussed, and the sensitivity, specificity, relative value, likelihood ratios, and accuracy for each were established. The performance of these criteria is included in Table 14.[27]

TABLE 11.—*Rare But Reported Manifestations of Adult-Onset Still's Disease*

Central nervous system
Peripheral neuropathy
Adult respiratory distress syndrome
Congestive heart failure
Disseminated intravascular coagulopathy
Thrombocytopenia
Subcutaneous nodules
Necrotizing lymphadenopathy

How does the patient's illness in this case presentation fit into the criteria described above? First and foremost, after a thorough evaluation, the patient was without evidence of infection, cancer, or rheumatic disease. Her clinical course suggests that she meets all of the major and minor criteria listed in Table 13. While this does not prove that the patient is suffering from adult-onset Still's disease, it suggests that it is the most appropriate diagnosis, given her clinical presentation and course. Although it may appear that it took too long to reach this conclusion, it is important to realize that the mean delay in reaching the diagnosis recorded in the literature is as long as 16 months.[18] In retrospect, our patient appears to have manifested the classic symptoms, signs, and laboratory features of adult-onset Still's disease. Even if it had been clear from the beginning that she might be suffering from Still's disease, the diagnosis could not have been made until all the other possible causes had been adequately excluded. The difficulty in arriving at this diagnosis highlights the fact that adult-onset Still's disease is poorly understood, and even among physicians and the medical community, it is not well recognized. While her hospital course was severe and troubling, other similar cases have been reported in the literature.[24] Fortunately, this patient responded to the aggressive interventions undertaken by her physicians,

TABLE 12.—*Laboratory Findings in Patients With Adult-Onset Still's Disease, n = 288*

Laboratory Findings	*Patients, %*
ESR ≥40 mm/hour	96.7
Negative antinuclear antibody	93.2
Negative rheumatoid factor	92.4
Leukocytes ≥10 × 10^9/liter (≥10,000/mm^3)	91.7
Albumin ≤35 grams/liter (≤3.5 grams/dl)	80.0
Elevated hepatic enzymes	71.6
Hemoglobin <100 grams/liter (<10 grams/dl)	68.0
Leukocytes ≥18 × 10^9/liter (≥18,000/mm^3)	60.0
Neutrophils ≥0.90 (≥90%)	35.0

ESR = erythrocyte sedimentation rate
Adapted from Ohta et al.[17]

TABLE 13.—*Criteria* for the Classification of Adult-Onset Still's Disease*

Criteria	Description
Major	Fever to 39°C (102°F) >1 week
	Arthralgia >2 week
	Typical rash
	Leukocytosis (>10 × 10^9/l with >0.80 neutrophils)
Minor	Sore throat
	Lymphadenopathy with or without splenomegaly
	Liver dysfunction
	Negative rheumatoid factor and antinuclear antibody tests
Exclusions	Infections
	Malignant neoplasms
	Rheumatic diseases

*Five or more criteria, including two or more major criteria, are required for the classification of adult-onset Still's disease.
Adapted from Yamaguchi et al.[27]

TABLE 14.—*Performance of Criteria for Adult-Onset Still's Disease**

Application of Eight Criteria	Sensitivity, %	Specificity, %
When criteria given equal weight		
≥4 Criteria	100.0	75.0
≥5 Criteria	96.2	89.6
≥6 Criteria	83.0	98.2
When divided into four major and four minor criteria		
≥2 Major and ≥2 minor	98.1	85.4
Total ≥4 with ≥2 major	100	84.1
Total ≥5 with ≥2 major	96.2	92.1

Adapted from Yamaguchi et al.[27]
*The data reflect the application of criteria to 53 patients with definite Still's disease and 164 control patients.

and at the time this report was compiled, 12 weeks after discharge, she appears to be doing well. She has responded well to a slow and gradual reduction in the dosage of her oral glucocorticoid and has not required the use of a second-line agent.

What is the appropriate treatment of this disorder once the diagnosis is made? Because there is no known cause, treatment is empirical. Still's disease is frequently a self-limited illness that follows a remitting course. Thus, the treatment course in many patients need not be a long one. Patients will often follow a polycyclic pattern with remissions and exacerbations.[21] Nonsteroidal anti-inflammatory drugs (NSAIDs) have classically been described as the first-line treatment option; yet, the literature suggests that high-dose salicylates or NSAIDs are effective in only 20% of patients.[19,22] Patients for whom NSAID therapy fails and those with severe disease will need glucocorticoid therapy. Prednisone should be given in a dose of 1 to 2 mg per kg a day, although some patients may do well with smaller doses. For those patients with severe disease and those who cannot be successfully tapered off glucocorticoids, alternative agents need to be considered. In those with persistent mild disease, despite adequate trials of glucocorticoids, or those who have a flare while the drug doses are being tapered, hydroxychloroquine sulfate has been advocated as a useful adjunct. In addition, intramuscular gold salts, sulfasalazine (salazopyridine), and penicillamine have all been used in patients with persistent disease. The most-often-used second-line agent has been intramuscular gold; this has been associated with a 40% improvement rate.[19] More recently, methotrexate has been useful for articular and systemic manifestations of adult-onset Still's disease and has been a useful "steroid-sparing" agent.[18,26] Azathioprine and cyclophosphamide have been used, but their use should only be considered in cases of severe or refractory disease.[30,31]

How about prognosis? Most patients do well with only limited functional disability from their disease.[16,23] A small fraction will go on to have serious arthritis and ankylosis. This subset can often be identified relatively early as those with polyarticular onset, hip involvement, and disease requiring glucocorticoid therapy for longer than two years.[23] A retrospective series designed to assess the long-term prognosis in patients with Still's disease compared patients with a mean duration of disease of 10 years with same-sex sibling controls. Of patients 5 or more years from the initial diagnosis, 50% were no longer taking medication. Patients with Still's disease were found to have higher levels of pain, physical disability, and psychological disability than controls; however, the levels of pain and disability were low when compared with those of other rheumatic diseases.[32]

The patient discussed in this review suffered from a progressive, indolent disorder that provided a substantial diagnostic dilemma for those involved in her care. She underwent an extensive diagnostic evaluation, and only through a process of exclusion was the appropriate diagnosis reached. Although she did undergo bilateral silicone gel breast implantation before the onset of the disorder, there is little anecdotal or epidemiologic evidence to support that she had a systemic connective tissue disease related to the breast implantation. What this patient did suffer from was a systemic inflammatory illness accompanied by spiking fevers, rash, and polyarthritis. Based on the constellation of symptoms, signs, and laboratory data, it appears that she had adult-onset Still's disease. Her lack of polyarticular onset, no hip involvement, and a good response to steroid therapy with a relatively quick taper of the dosage all suggest that she will have a good functional outcome.

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